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Procedural and Physical Interventions for Vaccine Injections

Systematic Review of Randomized Controlled Trials and Quasi-Randomized Controlled Trials

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Background: This systematic review evaluated the effectiveness of physical and procedural interventions for reducing pain and related outcomes during vaccination.

Design/Methods: Databases were searched using a broad search strategy to identify relevant randomized and quasi-randomized controlled trials. Data were extracted according to procedure phase (preprocedure, acute, recovery, and combinations of these) and pooled using established methods.

Results: A total of 31 studies were included. Acute infant distress was diminished during intramuscular injection without aspiration (n = 313): standardized mean difference (SMD) −0.82 (95% confidence interval [CI]: −1.18, −0.46). Injecting the most painful vaccine last during vaccinations reduced acute infant distress (n = 196): SMD −0.69 (95% CI: −0.98, −0.4). Simultaneous injections reduced acute infant distress compared with sequential injections (n = 172): SMD −0.56 (95% CI: −0.87, −0.25). There was no benefit of simultaneous injections in children. Less infant distress during the acute and recovery phases combined occurred with vastus lateralis (vs. deltoid) injections (n = 185): SMD −0.70 (95% CI: −1.00, −0.41). Skin-to-skin contact in neonates (n = 736) reduced acute distress: SMD −0.65 (95% CI: −1.05, −0.25). Holding infants reduced acute distress after removal of the data from 1 methodologically diverse study (n = 107): SMD −1.25 (95% CI: −2.05, −0.46). Holding after vaccination (n = 417) reduced infant distress during the acute and recovery phases combined: SMD −0.65 (95% CI: −1.08, −0.22). Self-reported fear was reduced for children positioned upright (n = 107): SMD −0.39 (95% CI: −0.77, −0.01). Non-nutritive sucking (n = 186) reduced acute distress in infants: SMD −1.88 (95% CI: −2.57, −1.18). Manual tactile stimulation did not reduce pain across the lifespan. An external vibrating device and cold reduced pain in children (n = 145): SMD −1.23 (95% CI: −1.58, −0.87). There was no benefit of warming the vaccine in adults. Muscle tension was beneficial in selected indices of fainting in adolescents and adults.

Conclusions: Interventions with evidence of benefit in select populations include: no aspiration, injecting most painful vaccine last, simultaneous injections, vastus lateralis injection, positioning interventions, non-nutritive sucking, external vibrating device with cold, and muscle tension.

Key Words: pain management, randomized controlled trial, systematic review, vaccination, injection techniques

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Vaccine injections are the most frequent painful medical procedure performed worldwide. Numerous interventions have been evaluated to combat the pain from vaccine injections.[1] These interventions can be broadly divided into pharmacological, psychological, procedural, and physical approaches. But for the costs of training clinicians, the majority of procedural and physical interventions offer the advantage of being time and resource cost neutral when compared with other approaches, and hence can be applied across clinical settings.

In a previous knowledge synthesis on this topic, we found support for several different procedural and physical

interventions.[2] These interventions were subsequently incorporated in a clinical practice guideline about childhood vaccination pain management.[1] Since the original guideline was developed, additional research has been undertaken that has the potential to impact previous conclusions. In addition, the original guideline excluded research in adults, leaving a gap in best practices for this population. The current systematic review was therefore undertaken to update and expand the knowledge synthesis on this topic.[3]

This manuscript reports the results for the effects of the following procedural and physical interventions: (1) aspiration during intramuscular (IM) vaccine injection, (2) order of injection for sequential vaccine injections, (3) simultaneous versus sequential injection of multiple vaccines, (4) positioning of the individual undergoing vaccination, (5) anatomic location for the vaccine injection, (6) non-nutritive sucking during vaccination, (7) tactile stimulation (manual and vibration) during vaccination, (8) warming the vaccine, and (9) muscle tension (for individuals with a history of fainting). Breastfeeding, which combines physical (positioning and non-nutritive sucking) and pharmacological (sweet-tasting substances) elements, is included in a separate manuscript in this series.[4] Similarly, we also separately report on the effects of combined interventions that include physical interventions (eg, non-nutritive sucking and sweet-tasting substances together) and the effectiveness of muscle tension in individuals with high levels of needle fear and a history of fainting.[4,5]

METHODS

A universal approach was used to carry out several systematic reviews on the same topic; the methodological details are provided elsewhere.[3] Briefly, both the Grading of Assessments, Recommendations, Development and Evaluation (GRADE)[6] and Cochrane[7] methodologies guided the review. The search strategy was developed with the assistance of an academic librarian and was executed in EMBASE, Medline, PsycINFO, CINAHL, and ProQuest Dissertations & Theses Global. Relevant citations were screened and included as previously described.[3]

The review included individuals of all ages undergoing vaccination in any setting or if not undergoing vaccination, the closest related skin-breaking procedure or context (eg, venipuncture) and randomized or quasi-randomized study designs. We included studies published as a full report or short report and published academic theses. The included interventions, critical outcomes, and important outcomes included in the review were identified from a national multidisciplinary team, Help ELiminate Pain in Kids & Adults (HELPinKids&Adults), originally assembled for the specific purpose of undertaking knowledge translation activities in

TABLE 1. Clinical Questions and Outcomes

Clinical Question	Critical Outcomes*	Important Outcomes
Procedural interventions		
Should no aspiration be used (rather than aspiration) during intramuscular vaccine injections in individuals of all ages?	Pain, distress	Procedure outcome, compliance, satisfaction, preference
Should injecting the most painful vaccine last be used (rather than first) during vaccine injections in individuals of all ages?	Pain, distress	Procedure outcome, compliance, satisfaction, preference
Should simultaneous injections be used (rather than sequential injections) during vaccine injections in infants 0-1 y?	Distress	Procedure outcome, parent fear, compliance, preference, satisfaction
Should simultaneous injections be used (rather than sequential injections) during vaccine injections in children above 1-10 y?	Pain, distress	Fear, procedure outcome, parent fear, compliance, memory, preference, satisfaction
Should the vastus lateralis be used (rather than the deltoid) as the site of injection during vaccine injections in infants 0-11 mo?	Distress	Procedure outcome, safety, compliance, preference, satisfaction
Physical interventions		
Should skin-to-skin contact be used during vaccine injections in neonates 0-1 mo?	Distress	Procedure outcome, parent fear, use of intervention, compliance, preference, satisfaction
Should holding be used (rather than lying supine) during vaccine injections in children 0-3 y?	Distress	Procedure outcome, parent fear, use of intervention, compliance, preference, satisfaction
If holding is not used during vaccine injections, should a combined holding intervention (including patting and/or rocking) be used after vaccine injections in children 0-3 y?	Distress	Procedure outcome, parent fear, use of intervention, compliance, preference, satisfaction
Should sitting upright be used (rather than lying supine) during vaccine injections in children above 3 y and adults?	Pain, fear	Distress, procedure outcome, parent fear, use of intervention, compliance, memory, preference, satisfaction
Should non-nutritive sucking (using a finger/thumb, pacifier) be used during vaccine injections in children 0-2 y?	Distress	Procedure outcome, parent fear, use of intervention, compliance, preference, satisfaction
Should manual tactile stimulation be used during vaccine injections in individuals of all ages?	Pain, distress	Fear, procedure outcome, use of intervention, compliance, preference, satisfaction
Should tactile stimulation using an external vibrating device and cold be used during vaccine injections in children above 3-17 y?	Pain, fear	Distress, procedure outcome, use of intervention, compliance, preference, satisfaction
Should warming the vaccine before vaccine injections be used in individuals of all ages?	Pain, distress	Preference, satisfaction
Should muscle tension be used for vaccine injections in children 7 y and above and adults with a history of fainting?	Fainting	Pain, distress, fear, procedure outcome, compliance, memory, preference, satisfaction

*Distress is the critical outcome in the absence of data for pain and/or fear in individuals incapable of self-report (eg, infants).

this therapeutic area.[3] Outcomes that were identified as critically important and important to decision making were extracted, as available in included studies. Pain was typically prioritized as the critically important outcome, defined as self-report of pain during vaccination. Distress was accepted as the critically important outcome in patient populations for which self-report was not possible (eg, infants) and was additionally considered in populations for which self-report could be unreliable (eg, children below 7 y). Distress was defined as observer-rated behavior of an individual's response during vaccination. Additional critical outcomes included fear and fainting, depending on the intervention under evaluation.[3] A list of included clinical questions and critically important and important outcomes is shown in Table 1.

The Cochrane risk of bias tool (https://bmg.cochrane.org/assessing-risk-bias-included-studies) was used to evaluate methodological limitations and the RevMan software program (version 5.2, Cochrane Collaboration, Copenhagen, Denmark) was used to pool the data. The effect of each intervention was expressed as a standardized mean difference (SMD) with accompanying 95% confidence interval (CI) or relative risk (RR) and CI, as appropriate. A random effects model was used for all analyses. Statistical heterogeneity was assessed using I^2 and χ^2 tests.[3]

As previously reported,[3] to more precisely describe the effects of the intervention, outcomes that were evaluated at multiple time-points were analyzed according to the procedure phase: (1) the preprocedure phase, which occurred postintervention but before vaccine injection(s); (2) the acute procedure phase (within the first minute of needle puncture and vaccine injection); and (3) the recovery procedure phase (1 to 5 min after vaccine injection(s)). Late onset pain at the injection site (ie, pain occurring hours to days after injection), was not examined.

Data from multiple observers assessing the same outcome (eg, parent-rated child distress, clinician-rated child distress) and data from multiple time-points within the same procedure phase (eg, acute distress measured every 15 s within the first minute of vaccine injection) were pooled before inclusion in the meta-analysis using established methods.[8] An emphasis was placed on the effects of an intervention during the acute procedure phase.

Means and SDs were calculated from medians, ranges, SEs, and 95% CI or estimated from graphs. Authors of trials were contacted for further details and provision of original data if the published report contained insufficient information. Modification of original data was done (eg, range conversion to SD) on a very restricted predefined basis, as needed, according to established methods.[9]

Separate analyses were conducted to account for developmental stage, attributes of the intervention, or both. For simultaneous injections, infants were analyzed separately from children. For positioning interventions, the effects of skin-to-skin contact were analyzed in neonates while holding was analyzed in infants and sitting upright was analyzed in children. Holding interventions applied postvaccination were analyzed separately from holding during vaccination. Finally, tactile stimulation was analyzed according to whether it was delivered manually or with an external vibrating device. Analyses are presented according to these a priori decisions. In addition, analyses were carried out to examine the effects of including and excluding studies of low study methodology and/or to examine heterogeneity.

Evidence profiles and summary of findings tables were created using the GRADE profiler software (version 3.6.1) in which all judgments pertaining to evaluation of quality of evidence were recorded. When findings demonstrated a benefit across critical outcomes, the intervention was said to have benefit across all measured outcomes. When the results were inconsistent across all measured outcomes, the results were said to be "mixed." Interventions without statistical evidence of benefit were said to have no evidence of a benefit.

RESULTS

A total of 114,251 citations were retrieved from the databases. Another 138 were identified separately from manual searches of various sources (eg, reference lists). All citations were saved in an EndNote library that identified 32,155 duplicates. The remaining 82,234 citations were reviewed by 2 of the authors (A.T., V.S.) against the inclusion criteria.[3] Thirty-seven studies investigating procedural and physical interventions were included in the review.[10–46] In 6 cases, multiple citations were identified for the same study; 3 of them included a dissertation[41–43] and published manuscript of the same data,[20,30,33] and the other 3 included multiple citations[44–46] to the same study.[27] The profile summarizing the trial flow is shown in Figure 1.

Characteristics of included trials are displayed in Table 2. Excluded studies included: (1) combined interventions versus control (n = 1)[47]; (2) head-to-head comparisons (n = 2)[48,49]; (3) studies that did not include interventions according to the clinical question (n = 2)[50,51]; and (4) studies with insufficient data (n = 2).[52,53] Altogether, 28 studies utilized a between-groups (parallel) design; the remaining 3 used a cross-over design. In 1 cross-over study,[11] only the results from the first day were included; hence, mimicking a between-groups design. All studies provided data for 2 or more treatment arms. Four studies included adults, 24 included children, and 3 included both adults and children.

Quality of Studies and Risk of Bias

Table 3 shows the results for the risk of bias assessment for critical outcomes. All trials had a high overall risk of bias primarily due to lack of blinding of important personnel.

Overall Quality of Evidence and Treatment Effects

A quantitative summary of the treatment effects for available critical outcomes is provided below, according to the clinical question; a qualitative summary is displayed in Table 4. Supporting GRADE Evidence Profiles and Summary of Findings tables (see Tables, Supplemental Digital Content 1 to 14, http://links.lww.com/CJP/A282, http://links.lww.com/CJP/A283, http://links.lww.com/CJP/A284, http://links.lww.com/CJP/A285, http://links.lww.com/CJP/A286, http://links.lww.com/CJP/A287, http://links.lww.com/CJP/A288, http://links.lww.com/CJP/A289, http://links.lww.com/CJP/A290, http://links.lww.com/CJP/A291, http://links.lww.com/CJP/A292, http://links.lww.com/CJP/A293, http://links.lww.com/CJP/A294, http://links.lww.com/CJP/A295) and accompanying Forest plots (see Figures, Supplemental Digital Content 1-14, http://links.lww.com/CJP/A296, http://links.lww.com/CJP/A297, http://links.lww.com/CJP/A298, http://links.lww.com/CJP/A299, http://links.lww.com/CJP/A300, http://links.lww.com/CJP/A301, http://links.lww.com/CJP/A302, http://links.lww.com/CJP/A303, http://links.lww.com/CJP/A304, http://links.lww.com/CJP/A305, http://links.lww.com/CJP/A306, http://links.lww.com/CJP/A307, http://links.lww.com/CJP/A308, http://links.lww.

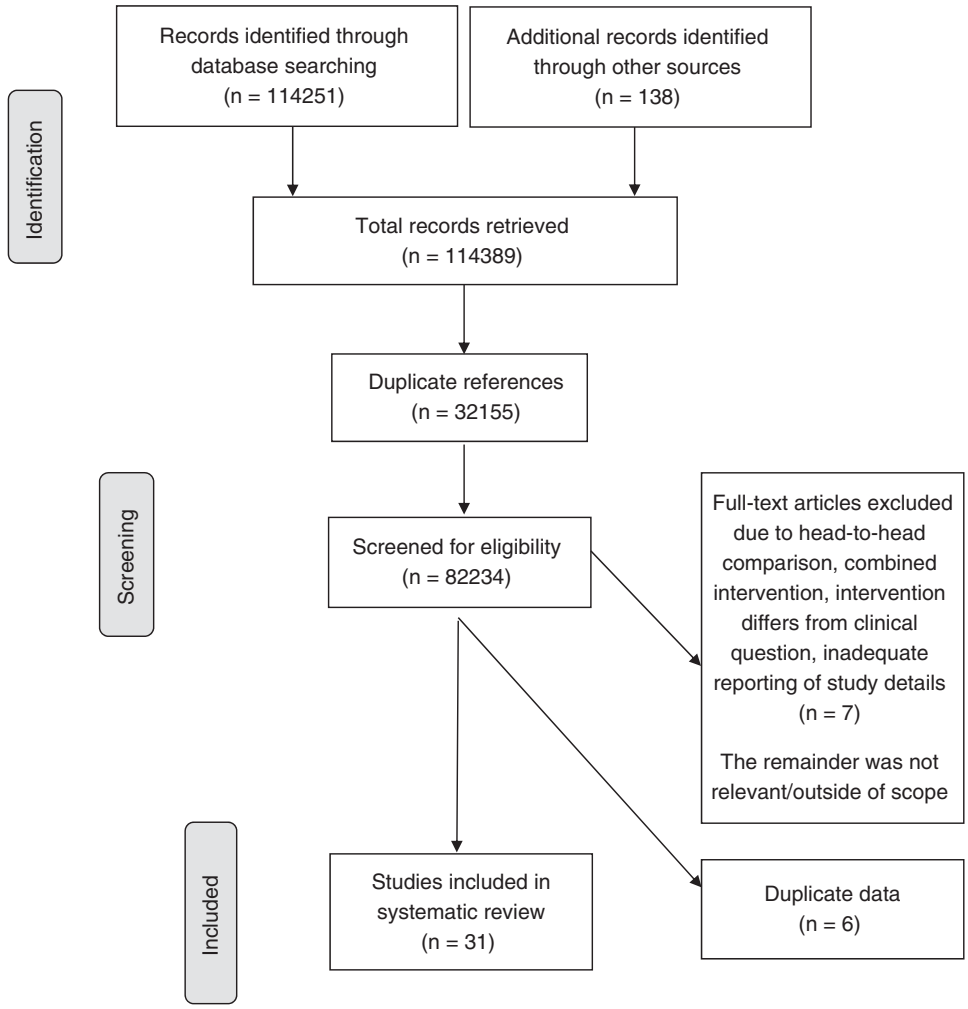

FIGURE 1. Flow of studies.

com/CJP/A309) for critically important and important outcomes are included as Supplemental Digital Content.

Should No Aspiration be Used (Rather Than Aspiration) During IM Injections in Individuals of All Ages?

Three trials including infants, children, and adults investigated the effects of not aspirating before IM vaccine injections.[10–12] There was very low quality of evidence and the results were mixed (see Table, http://links.lww.com/CJP/A282 and Figure, http://links.lww.com/CJP/A296 SDC 1). In one of the studies including 114 children and adults, there was no evidence of a benefit for individuals vaccinated in the absence of aspiration versus those vaccinated with aspiration: SMD 0.28 (95% CI: −0.12, 0.68). In the other 2 studies including 313 infants, however, levels of acute distress were lower in those who received fast injections without aspiration compared with those who received slow injections with aspiration: SMD −0.82 (95% CI: −1.18, −0.46). Either a benefit or no difference was observed for other indicators of distress. It was not clear whether differences between groups were obscured in the former analysis by an insufficient duration of time allocated for aspiration, variability in the anatomic injection site, or the specific vaccine being administered to the participants. Injection speed was a potential confounder in the latter analysis.

Should Injecting the Most Painful Vaccine Last be Used (Rather Than First) During Vaccine Injections in Individuals of All Ages?

Two trials including infants in the first 6 months of life investigated the effect of injecting the most painful vaccine last.[13,14] Included studies compared either: (1) pneumococcus conjugate vaccine, PCV (Prevnar) to diphtheria and tetanus toxoids, polio, acellular pertussis, and *Haemophilus influenzae* type b conjugate vaccine, DPTaP-Hib (Pentacel), or (2) Bacille Calmette-Guérin vaccine, BCG (Tubervac) to hepatitis B vaccine (GeneVac-B). There was moderate quality evidence for distress, the critical outcome (see Table, http://links.lww.com/CJP/A283 SDC 2). When given first, PCV and hepatitis B caused more pain than DPTaP-Hib and BCG, respectively. Administering the most painful vaccine last (ie, PCV after DPTaP-Hib and hepatitis B after BCG, respectively) caused lower overall infant acute distress for both injections (n = 196): SMD −0.69 (95% CI: −0.98, −0.40) (see Table http://

TABLE 2. Characteristics of the Trials Included in the Systematic Review

Author, Year, Country	Injection Details	Population, Enrolled, Design, Setting	Intervention, Sample Size*	Critical Outcomes
Procedural interventions				
Should no aspiration be used (rather than aspiration) during intramuscular vaccine injections in individuals of all ages?				
Girish & Ravi 2014,[11] India	DTwP 0.5 mL IM; 24-G, 1-inch needle; 90-degree angle; anterolateral thigh	N = 200; children 6 wk-18 mo; between-groups design; single center, hospital	Rapid injection without aspiration (n = 100) or Slow injection with aspiration (n = 100)	Distress: MBPS, cry
Ipp et al 2007,[10] Canada	DPTaP-Hib 0.5 mL IM; 25-G, 22-mm needle; 90-degree angle; anterolateral thigh	N = 113; infants 4-6 mo; between-groups design; single center, primary care practice	Rapid injection (1-2 s) without aspiration (n = 56) or Slow injection (5-10 s) with aspiration (n = 57)	Distress: MBPS, VAS, cry
Petousis-Harris et al 2013 (1,2),[12] New Zealand	HPV (Gardasil); 23-G, 25-mm needle; 90-degree angle; deltoid	N = 114; women 14-45 y and men 14-26 y; cross-over design;† clinics at the School of Population Health	Rapid injection without aspiration (< 1 s) (n = 34) or Slow without aspiration (5-10 s) (n = 45) or Slow with aspiration (5-10 s) (n = 35)	Pain: VAS
Should injecting the most painful vaccine last be used (rather than first) during vaccine injections in individuals of all ages?				
Ipp et al 2009,[13] Canada	DPTaP-Hib (Pentacel), PCV (Prevnar); 0.5 mL/vaccine IM; 25-G, 22-mm needle; 90-degree angle; anterolateral thigh, 1-2 s; alternate limbs for each injection	N = 120; infants 2-6 mo; between-groups design; single center, primary care practice	DPTaP-Hib (Pentacel) first, then PCV (Prevnar) (n = 60) or PCV first, then DPTaP-Hib (n = 60)	Distress: MBPS, VAS, cry
Ravikiran et al 2011,[14] India	Hepatitis B 0.5 mL IM; 23-G, 25-mm needle; anterolateral thigh; BCG 0.1 mL ID; 26-G, 13-mm needle; left shoulder	N = 76; newborns; between-groups design; single center, hospital vaccination room	BCG (Tubervac) first, then Hepatitis B (GeneVac-B) (n = 38) or Hepatitis B first, then BCG (n = 38)	Distress: NIPS, VAS
Should simultaneous injections be used (rather than sequential injections) during vaccine injections in infants 0-1 y?				
Hanson et al 2010,[15] Canada	DPTP-Hib, Hepatitis B, PCV; no injection details	N = 101; infants 4 mo; between-groups design; multicenter, community health clinics	Simultaneous injection: first 2 vaccines given simultaneously then third given up to 15 s later (n = 49) or Sequential injection: all 3 vaccines given sequentially with up to 15 s between each injection (n = 50)	Distress: NIPS
McGowan et al 2013,[16] UK	DTaP-IPV-Hib + PCV or DTaP-IPV-Hib + MenC; IM; 23-G 25-mm needle; 90-degree angle; anterolateral thigh, 1-2 s no aspiration; DTaP-IPV-Hib in right thigh	N = 73; infants 2-6 mo; between-groups design; single center, primary care practice	Simultaneous injection: 2 injections were given and could be either DTaP/IPV/Hib and PCV or DTaP/IPV/Hib and MenC (n = 37) or Sequential injection: 2 injections were given and could be either DTaP/IPV/Hib and PCV or DTaP/IPV/Hib and MenC (n = 36)	Distress: MBPS, VAS

(*Continued*)

TABLE 2. (*continued*)

Author, Year, Country	Injection Details	Population, Enrolled, Design, Setting	Intervention, Sample Size*	Critical Outcomes
Should simultaneous injections be used (rather than sequential injections) during vaccine injections in children above 1-10 y?				
Horn and McCarthy 1999,[17] USA	DPT and MMR; no injection details	N = 46; children 4-6 y; between-groups design; single center, primary care practice	Simultaneous injection (n = 24) or Sequential injection (n = 22)	Pain: Wong-Baker FACES scale
Should the vastus lateralis be used (rather than the deltoid) as the site of injection during vaccine injections in infants 0-11 mo?				
Celebioglu et al 2010,[18] Turkey	DTP 0.5 mL IM; 24- or 25-G needle; 90-degree angle; 10 s	N = 185; infants 4 mo; between-groups design; primary care practice	Vastus lateralis IM injection (n = 95) or Deltoid IM injection (n = 90)	Distress: NIPS, cry
Physical interventions				
Should skin-to-skin contact be used during vaccine injections in neonates 0-1 mo?				
Chermont et al 2009 (1,2),[19] Brazil	Hepatitis B 0.5 mL IM; 25-G needle; anterolateral thigh	N = 640; newborn 12-72 h; between-groups design; single center, hospital maternity ward	Mother holding diaper-clad neonate on chest (skin-to-skin) + 1 mL water 2 min before, during, and 2 min after procedure (n = 160) or Diaper-clad neonate in crib + 1 mL water (n = 160) or Mother holding diaper-clad neonate on chest (skin-to-skin) + 1 mL dextrose 25% solution 2 min before, during, and 2 min after procedure (n = 160) or Diaper-clad neonate in crib + 1 mL dextrose 25% solution (n = 160)	Distress: NFCS, NIPS, PIPP
Kostandy et al 2013[20] (same as Kostandy 2005 thesis[41]), USA	Hepatitis B IM; anterolateral thigh	N = 36; newborns second day of life; between-groups design; single center, hospital maternity ward	Mother holding diaper-clad neonate on chest (skin-to-skin) with blanket over top for 15-20 min before and 6 min after injection (n = 17) or Neonate clothed, supine, with blanket over top (n = 19)	Distress: cry
Saeidi et al 2011,[21] Iran	Vaccine NR; no injection details	N = 60; newborns after first day of life; between-groups design; single center, hospital maternity ward	Mother holding neonate on chest (duration unclear—2 or 30 min) before, during, and 3 min after procedure (n = 30) or Neonate supine wrapped in blanket aside mother's bed (n = 30)	Distress: NIPS
Should holding be used (rather than lying supine) during vaccine injections in children 0-3 y?				
Hallstrom 1968,[22] USA	Vaccine NR; lateral aspect of thigh	N = 31; infants 6-26 wk; between-groups design; single center,	Mother holding infant firmly and closely against	Distress: cry

(*Continued*)

TABLE 2. (*continued*)

Author, Year, Country	Injection Details	Population, Enrolled, Design, Setting	Intervention, Sample Size*	Critical Outcomes
		university hospital clinic	the body during injection in a position deemed comfortable by the mother (n = 15) or Infant supine (n = 16)	
Ipp et al 2004,[23] Canada	DPTP 0.5 mL IM; 25-G, 16-mm needle; anterolateral thigh	N = 106; infants 2-6 mo; between-groups design; single center, primary care practice	Mother holding infant during injection in a position deemed comfortable by mother while standing (n = 56) or Infant supine (n = 50)	Distress: NFCS, cry
Taavoni et al 2010,[44] Iran (same as Taavoni et al 2009,[46] Taavoni 2010a,[27] and Shah Ali et al 2009[45]), Iran	DPT 0.5 mL; 23-G, 2.5 cm needle	N = 152; infants 2-4 mo; between-groups design; multicenter, primary care practices	Pacifier 2 min before, during, and 15 s postinjection (n = 38)‡ or Infant supine (n = 38) or Mother holding infant starting 2 min before, during, and 15 s postinjection (n = 38) or Breastfeeding starting 2 min before, during, and 15 s after injection (n = 38)‡	Distress: MBPS
If holding is not used during vaccine injections, should a combined holding intervention (including patting and/or rocking) be used after vaccine injections in children 0-3 y?				
Chou et al 2012,[24] China	BCG or hepatitis B; no injection details	N = 187; newborns 1-2 d; between-groups design; single center, hospital	Music starting 10 min before procedure and music + nurse cuddling in upright position and back-patting immediately postinjection for 3 min (n = 88) or Control (infants held transversely after procedure and gently patted on buttocks and returned to crib; caregivers able to provide comfort) (n = 99)	Distress: NFCS, VAS, MAISD
Harrington et al 2012 (1,2),[25] USA	Hepatitis B, DTP-IPV-Hib, PCV; 0.5 mL/vaccine IM; 23-G, 1.59-cm needle; anterolateral thigh; sequential injections	N = 230; infants 2-4 mo; between-groups design; single center, hospital clinic	Water + control (no intervention) (n = 56) or Sucrose + control (n = 58) or Water + combined physical intervention (swaddling, side/stomach position, shushing, swinging, and sucking) (n = 58) or Sucrose + combined physical intervention	Distress: Modified Riley Pain Scale

(*Continued*)

TABLE 2. (*continued*)

Author, Year, Country	Injection Details	Population, Enrolled, Design, Setting	Intervention, Sample Size*	Critical Outcomes
			(as described above) (n = 58)	
Should sitting upright be used (rather than lying supine) during vaccine injections in children above 3 y and adults?				
Lacey et al 2008,[26] USA	MMR, DTaP, and IVP; sequential injection	N = 108; children 4-6 y; between-groups design; single center, pediatric clinic in a hospital	Sitting up before injection (n = 52) or Supine position (n = 55)	Fear: Fearometer Pain: Wong-Baker FACES Scale
Should non-nutritive sucking (eg, finger/thumb, pacifier) be used during vaccine injections in children 0-2 y?				
Liaw et al 2011 (1),[28] China	Hepatitis B vaccine IM; 90-degree angle; vastus lateralis; aspiration before injection	N = 165; newborns after second to third day of life; between-groups design; single center, nursery in a hospital	Non-nutritive sucking using standard silicone newborn pacifier 2 min preinjection (n = 55) or Control (gentle touch and verbal comfort) (n = 55) or Sucrose 20% 2 mL using a syringe 2 min preinjection (n = 55)‡	Distress: NFCS, cry
Taavoni 2010a (1),[27] Iran (same as Taavoni et al 2009,[46] 2010,[44] and Shah Ali et al 2009[45]), Iran	DPT 0.5 mL; 23-G, 2.5-cm needle	N = 152; infants 2-4 mo; between-groups design; multicenter, primary care practices	Pacifier 2 min before, during, and 15 s postinjection (n = 38) or No treatment (infant supine) (n = 38) or Mother holding infant starting 2 min before, during, and 15 s postinjection (n = 38)‡ or Breastfeeding starting 2 min before, during and 15 s postinjection (n = 38)‡	Distress: MBPS
Should manual tactile stimulation be used during vaccine injections in individuals of all ages?				
Chung et al 2002,[29] China	Hepatitis A and Hepatitis B; IM; alternate arms	N = 74; university students; cross-over design; single center, university	Manual pressure on arm for 10 s preinjection by immunizer for first injection by immunizer (n = 74) or Control (n = 74)	Pain: Pain Intensity Verbal Rating Scale
Hogan et al 2014[30] (same as Hogan 2011 thesis[42]), Canada	DTaP-IPV-Hib first then PCV (brand of vaccine changed mid-way through study); IM rapid injection without aspiration; 25-G, 25-mm needle; alternate thighs	N = 120; infants 4-6 mo; between-groups design; single center, primary care practice	Rubbing skin on leg 15 s preinjection, during, and postinjection by parent (n = 60) or Control (n = 60)	Distress: MBPS, cry, VAS
Jose et al 2012,[31] India	DPT; vastus lateralis	N = 60; infants 14 wk; between-groups design; multicenter, medical college clinics	Tapping leg with finger × 2 min preinjection, during, and up to 1 min postinjection by immunizer (n = 30) or Control (n = 30)	Distress: Behavioral Observation Pain Scale
Nakashima et al 2013,[32] Japan		N = 693; adults above 20 y; between-groups	Manual pressure on arm for 10 s preinjection by	Pain: VAS, Faces scale

(*Continued*)

TABLE 2. (*continued*)

Author, Year, Country	Injection Details	Population, Enrolled, Design, Setting	Intervention, Sample Size*	Critical Outcomes
	Influenza vaccine SC; 26-G, 13-mm needle; arm	design; multicenter; rural clinics and general hospitals	immunizer (n = 334) or Control (n = 345)	
Sparks 2001 (1)[33] (same as Sparks 1998 thesis[43]), USA	DTP (n = 22) or DTaP (n = 83) ± oral polio (preinjection); 0.5 mL/vaccine IM; 22-G, 25-mm needle; vastus lateralis muscle, right, or left leg	N = 105; children 4-6 y; between-groups design; multicenter, school clinics and walk-in public health clinic	Stroking skin on leg before and during injection with instruction to "keep thinking about how nice that feels" by immunizer (n = 33) or Bubble blowing (n = 33)‡ or Control (n = 33)	Pain: Oucher Scale
Taddio et al 2014a,[34] Canada	Hepatitis B, DPTaP-Hib, PCV, MenC, or MMR; IM vaccines given rapidly without prior aspiration; 25-G, 22-mm needle; anterolateral thigh, left leg	N = 121; infants 1-12 mo; between-groups design; single center, primary care practice	Rubbing skin on leg 5-10 s preinjection, during, and 5-10 s postinjection by immunizer (n = 62) or Control (n = 59)	Distress: MBPS, cry, VAS
Should tactile stimulation using an external vibrating device and cold be used during vaccine injections in children above 3-17 y?				
Berberich and Landman 2009,[35] USA	DTaP, IPV, MMR; IM vaccines given first in 1 arm with 25-G, 5/8-inch needle; SC vaccine given in other arm with 26-G, 5/8-inch needle	N = 41; children 4-6 y; between-groups design; single center, primary care practice	Application of a vibrating device on the contralateral arm which the child was directed to observe as it was moved toward the elbow; application of cold (ie, vapocoolant spray—ethyl chloride) on the ipsilateral arm and application of an external (nonvibrating) tactile stimulation device below the injection site (n = 20) or Control (n = 21)	Pain: FPS-R
Canbulat et al 2015,[36] Turkey	DTaP IM; left or right deltoid	N = 104; children 7 y; between-groups design; multicenter, schools	Application of a vibrating device and cold (ie, ice pack) (Buzzy) on the ipsilateral arm about 5 cm above the site of injection just before and during injection (n = 52) or Control (n = 52)	Pain: Wong-Baker FACES Scale, VAS Fear: CFS
Should warming the vaccine before vaccine injections be used in individuals of all ages?				
Maiden et al 2003,[37] Australia	ADT 0.5 mL IM, no aspiration; 23-G, 25-mm needle; 60-degree angle; deltoid muscle	N = 150; children and adults 16 y and above; between-groups design; single center, hospital emergency room	No warming (n = 50) or Rubbed 1 min between palms of hands (n = 50) or Warmed in an incubator 37°C for 5 min (n = 50)	Pain: McGill Present Pain Intensity Questionnaire
Should muscle tension be used for vaccine injections in children 7 y and above and adults with a history of fainting?				
Brignole et al 2002,[38] Italy	NA "Procedure" was a tilt-table test	N = 23; adults 18 y and above (mean age, 55 y); history of recurrent fainting; cross-over	Muscle tension (isometric handgrip with contraction) (n = 19)	Fainting: fainting during procedure and postprocedure

(*Continued*)

TABLE 2. (*continued*)

Author, Year, Country	Injection Details	Population, Enrolled, Design, Setting	Intervention, Sample Size*	Critical Outcomes
		design; single center, hospital based	or Control (handgrip without contraction) (n = 19)	
van Dijk et al 2006,[39] the Netherlands	NA episodes of fainting in everyday life	N = 223; children and adults (16-70 y); history of recurrent fainting; between-groups design; multicenter, hospital based	Muscle tension (physical counter-pressure maneuvers: leg crossing, arm tensing, handgrip; held for the longest tolerated time or until no symptoms of fainting with transition to second or third maneuver as needed; taught through demonstration, practice with biofeedback and provision of photos) (n = 98) or Control (explanation of mechanisms of fainting, lifestyle modification tips, pamphlet) (n = 110)	Fainting: 12 mo follow-up (using self-report log): (1) time to fainting recurrence; (2) number of patients fainting; (3) number of episodes/patient
Vogele et al 2003,[40] UK	NA "Procedure" was a surgical film	N = 44; adults attending nonmedical university program (mean age, 22 y); 22 "fainters" and 22 "nonfainters"; between-groups design; single center, university research laboratory	Muscle tension for individuals with fainting (brief instruction and practice with tensing muscles × 7 min) (n = 11) or Muscle tension for individuals without fainting (brief instruction and practice with tensing muscles × 7 min) (n = 11)‡ or Control for individuals with fainting (verbal interaction with researcher × 7 min) (n = 11) or Control for individuals without fainting (verbal interaction with researcher × 7 min) (n = 11)‡	NA (this study was not included in the meta-analysis for critical outcomes)

Studies were identified using the following notation: "First Author" "Year of Publication" (eg, Taddio 2014). If studies contributed to multiple analyses, then "(#)" was added to enable their discernment (eg, Taddio 2014 [1]). If the same author published >1 study in the same year, then a lower case letter was added after the first article in the same year by the same author (eg, Taddio 2014a [1]).

*Includes maximum sample size for critically important outcomes.

†Data from the first day was included in the analysis; hence the study mimicked a between-groups (parallel) design.

‡Data not included in the analysis.

Route: IM, intramuscular; SC, subcutaneous. Outcomes: CFS, Children Fear Scale; Cry, cry duration; FPS-R, Faces Pain Scale-Revised; MAISD, Measure of Adult and Infant Soothing and Distress; MBPS, Modified Behavioral Pain Scale; NFCS, Neonatal Facial Coding System; NIPS, Neonatal Infant Pain Scale; PIPP, Premature Infant Pain Scale; VAS, visual analog scale. Vaccines: ADT, adult diphtheria-tetanus; BCG, Bacille Calmette Guerin; DPTaP-Hib/DTP-IPV-Hib/DPTP-Hib, diphtheria, polio, tetanus, acellular pertussis, and *Hemophilus influenzae* type b conjugate; DPTP, diphtheria, polio, tetanus, pertussis; DTaP, diphtheria, tetanus, acellular pertussis; DTP/DPT, diphtheria, tetanus, pertussis; DTwP, diphtheria, tetanus, whole cell pertussis; Hib, *Hemophilus influenzae* type b; HPV, human papilloma virus; IVP, inactivated polio virus; min, minute; MenC, meningococcal C; MMR, measles, mumps, rubella; mo, month; PCV, pneumococcal conjugate vaccine; s, seconds; y, year. Other: NA, not applicable; NR, not reported.

TABLE 3. Assessment of Risk of Bias of Included Trials for Critical Outcomes

Author, Year	Adequate Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data Addressed	Free of Selective Reporting	Free of Other Bias	Overall Risk
Procedural interventions								
Should no aspiration be used (rather than aspiration) during intramuscular vaccine injections in individuals of all ages?								
Girish & Ravi 2014[11]	Yes	No	No	Yes	No	Yes	Yes	High
Ipp et al 2007[10]	Yes	Yes	No	Yes	Yes	Yes	Yes	High
Petousis-Harris et al 2013 (1,2)[12]	Yes	Unclear	No	Yes	Yes	Yes	Unclear	High
Should injecting the most painful vaccine last be used (rather than first) during vaccine injections in individuals of all ages?								
Ipp et al 2009[13]	Yes	Yes	Yes	Yes	Yes	No	Yes	High
Ravikiran et al 2011[14]	Yes	Yes	Yes	Yes	Yes	No	Yes	High
Should simultaneous injections be used (rather than sequential injections) during vaccine injections in infants 0-1 y?								
Hanson et al 2010[15]	Yes	Yes	No	Yes	Yes	Yes	Yes	High
McGowan et al 2013[16]	Yes	Yes	No	No	Yes	Yes	Yes	High
Should simultaneous injections be used (rather than sequential injections) during vaccine injections in children above 1-10 y?								
Horn & McCarthy 1999[17]	Yes	Unclear	No	No	Yes	Yes	No	High
Should the vastus lateralis be used (rather than the deltoid) as the site of injection during vaccine injections in infants 0-11 mo?								
Celebioglu et al 2010[18]	Unclear	Unclear	No	No	Yes	Yes	Yes	High
Physical interventions								
Should skin-to-skin contact be used during vaccine injections in neonates 0-1 mo?								
Chermont et al 2009 (1,2)[19]	Yes	Unclear	No	No	Yes	No	Yes	High
Kostandy et al 2013[20] (thesis 2005)[41]	Yes	Unclear	No	Unclear	Yes	Yes	Yes	High
Saeidi et al 2011[21]	Unclear	Unclear	No	Yes	Yes	Yes	Yes	High
Should holding be used (rather than lying supine) during vaccine injections in children 0-3 y?								
Hallstrom 1968[22]	Yes	Unclear	No	Yes	Yes	Yes	Yes	High
Ipp et al 2004[23]	Unclear	Unclear	No	Yes	Yes	Yes	Yes	High
Taavoni et al 2010[44] (same as 2009,[46] Taavoni 2010a,[27] Shah Ali et al 2009[45])	No	No	No	No	Yes	Yes	Yes	High
If holding is not used during vaccine injections, should a combined holding intervention (including patting and/or rocking) be used after vaccine injections in children 0-3 y?								
Chou et al 2012[24]	Yes	Unclear	No	No	Yes	Yes	Yes	High
Harrington et al 2012 (1,2)[25]	Yes	Yes	No	No	Yes	No	No	High
Should sitting upright be used (rather than lying supine) during vaccine injections in children above 3 y and adults?								
Lacey et al 2008[26]	Unclear	Unclear	No	No	Yes	Yes	Yes	High
Should non-nutritive sucking be used during vaccine injections in children 0-2 y?								
Liaw et al 2011 (1)[28]	Yes	Unclear	No	Yes	Yes	Yes	Yes	High
Taavoni 2010a (1)[27] (same as 2009,[46] 2010,[44] Shah Ali et al 2009[45])	No	No	No	No	Yes	Yes	Yes	High
Should manual tactile stimulation be used during vaccine injections in individuals of all ages?								
Chung et al 2002[29]	Unclear	Unclear	No	No	Yes	Yes	Unclear	High
Hogan et al 2014[30] (thesis 2011[42])	Yes	Yes	No	Yes	Yes	No	Unclear	High
Jose et al 2012[31]	No	Unclear	No	No	Yes	Yes	Unclear	High
Nakashima et al 2013[32]	No	No	No	No	Yes	Yes	Yes	High
Sparks 2001 (1)[33] (thesis 1998[43])	No	No	No	No	Yes	Yes	Unclear	High
Taddio 2014a[34]	Yes	Yes	No	Yes	Yes	Yes	Unclear	High
Should tactile stimulation using an external vibrating device and cold be used during vaccine injections in children above 3-17 y?								
Berberich and Landman 2009[35]	Yes	Yes	No	No	Yes	Yes	Yes	High
Canbulat et al 2015[36]	Yes	Unclear	No	No	Yes	No	Unclear	High
Should warming the vaccine be used before vaccine injections in individuals of all ages?								
Maiden et al 2003[37]	Yes	Yes	No	Yes	Yes	Yes	Yes	High
Should muscle tension be used for vaccine injections in children 7 y and above and adults with a history of fainting?								
Brignole et al 2002[38]	Unclear	Unclear	No	Unclear	Yes	Yes	Yes	High
van Dijk et al 2006[39]	Unclear	Unclear	No	Yes	Yes	Yes	No	High
Vogele et al 2003[40]	Unclear	Unclear	No	No	Unclear	Unclear	No	High

TABLE 4. Summary of Results for Critically Important Outcomes

Clinical Questions	Critical Outcomes*	Benefit of Intervention†	Quality of Evidence‡
Procedural interventions			
Should no aspiration be used (rather than aspiration) during intramuscular vaccine injections in individuals of all ages?	Pain, distress	Mixed	Very low
Should injecting the most painful vaccine last be used (rather than first) during vaccine injections in individuals of all ages?	Distress	Yes	Moderate
Should simultaneous injections be used (rather than sequential injections) during vaccine injections in infants 0-1 y?	Distress	Mixed	Low
Should simultaneous injections be used (rather than sequential injections) during vaccine injections in children above 1-10 y?	Pain	No	Very low
Should the vastus lateralis be used (rather than the deltoid) as the site of injection during vaccine injections in infants 0-11 mo?	Distress	Mixed	Low
Physical interventions			
Should skin-to-skin contact be used during vaccine injections in neonates 0-1 mo?	Distress	Yes	Moderate
Should holding be used (rather than lying supine) during vaccine injections in children 0-3 y?	Distress	Yes§	Very low
If holding is not used during vaccine injections, should a combined holding intervention (including patting and/or rocking) be used after vaccine injections in children 0-3 y?	Distress	Yes	Low
Should sitting upright be used (rather than lying supine) during vaccine injections in children above 3 y and adults?	Pain, fear	Mixed	Low
Should non-nutritive sucking (using a finger/thumb, pacifier) be used during vaccine injections in children 0-2 y?	Distress	Yes	Low
Should manual tactile stimulation be used during vaccine injections in individuals of all ages?	Pain, distress	No	Very low
Should tactile stimulation using an external vibrating device and cold be used during vaccine injections in children above 3-17 y?	Pain, fear	Mixed	Low
Should warming the vaccine before vaccine injections be used in individuals of all ages?	Pain	No	Low
Should muscle tension be used for vaccine injections in children 7 y and above and adults with a history of fainting?	Fainting	Mixed	Very low

*Includes results for the critical outcomes that were evaluated in included studies only.

†The results for the effect of the intervention have been summarized across all evaluated critical outcomes, and are expressed using the following notation: Yes, benefit was observed across all evaluated critical outcomes; Mixed, benefit was observed for 1 or more but not all evaluated critical outcomes; No, no evidence of benefit was observed for any of the evaluated critical outcomes.

‡Reflects the lowest quality of evidence rating across all evaluated critical outcomes, whereby rankings range from high to moderate to low to very low.

§On the basis of the results after removal of 1 study with a high risk of bias; see text for details.

links.lww.com/CJP/A283 and Figure http://links.lww.com/CJP/A297, SDC 2).

Should Simultaneous Injections be Used (Rather Than Sequential Injections) During Vaccine Injection in Infants 0 to 1 Year?

Two studies including infants aged 2 to 6 months were included.[15,16] The quality of evidence for the critical outcome of distress was low and the results were mixed for different indicators of distress (see Table http://links.lww.com/CJP/A284 and Figure, http://links.lww.com/CJP/A298 SDC 3). In the only analysis that included data from both studies (n = 172), there was evidence for a reduction in acute distress in the simultaneous injection group: SMD −0.56 (95% CI: −0.87, −0.25). Either a benefit or no difference was observed for other indicators of distress.

Should Simultaneous Injections be Used (Rather Than Sequential Injections) During Vaccine Injection in Children Above 1 to 10 Years?

In 1 study including children aged 4 to 6 years,[17] there was no evidence of a benefit for pain from simultaneous injections (n = 44): SMD 0.31 (95% CI: −0.29, 0.90) (see Table http://links.lww.com/CJP/A285 and Figure, http://links.lww.com/CJP/A299 SDC 4). There was very low quality of evidence for this outcome (see Table, http://links.lww.com/CJP/A285 SDC 4).

Should the Vastus Lateralis be Used (Rather Than the Deltoid) as the Site of Injection During Vaccine Injections in Infants 0 to 11 Months?

One trial including 185 infants aged 4 months compared vaccine injections in the vastus lateralis versus the deltoid muscle.[18] The quality of the evidence was low and the results were mixed (see Table http://links.lww.com/CJP/A286 and Figure, http://links.lww.com/CJP/A300 SDC 5). Less distress was observed for the vastus lateralis site during the acute and recovery procedure phases combined: SMD −0.70 (95% CI: −1.00, −0.41); however, there was no difference between groups during the acute procedure phase: SMD 0.11 (95% CI: −0.18, 0.40).

Should Skin-to-Skin Contact be Used During Vaccine Injections in Neonates 0 to 1 Month?

Three randomized trials in 736 neonates investigated skin-to-skin contact (whereby diaper-clad infants are positioned between their mother's breasts) versus lying supine.[19–21] Skin-to-skin contact was initiated at least

2 minutes before vaccine injection(s). The quality of evidence was moderate and there was evidence of benefit of this intervention across different phases of the procedure (see Table http://links.lww.com/CJP/A287 and Figure, http://links.lww.com/CJP/A301 SDC 6). For acute procedural distress specifically, the SMD was −0.65 (95% CI: −1.05, −0.25). For the recovery procedure phase, the SMD was −0.89 (95% CI: −1.26, −0.52).

Should Holding be Used (Rather Than Lying Supine) During Vaccine Injections in Children 0 to 3 Years?

Three trials examined holding versus lying supine during injections in infants aged 6 weeks to 6 months.[22,23,44] Holding was carried out by a parent and was initiated before vaccine injection(s) and continued during and after injection(s). There was low to very low quality evidence across the different outcomes of distress (see Table, http://links.lww.com/CJP/A288 SDC 7). No significant benefit of holding was observed (n = 213): SMD −0.72 (95% CI: −1.95, 0.51); however, in 1 included study, there was contamination of the control (lying supine) group whereby parents picked up infants immediately after vaccinations.[23] Removal of the data from this study altered the results for acute distress; infants in the holding group had lower levels of distress compared with infants in the supine group: SMD −1.25 (95% CI: −2.05, −0.46). The results were not significant for other distress outcomes; although data were obtained by the same methodologically diverse study (see Table http://links.lww.com/CJP/A288 and Figure, http://links.lww.com/CJP/A302 SDC 7).

If Holding is Not Used During Vaccine Injections, Should a Combined Holding Intervention (Including Patting and/or Rocking) be Used After Vaccine Injections in Children 0 to 3 Years?

Two studies in infants aged 1 day to 4 months examined holding interventions after injections in infants lying supine during vaccination.[24,25] The holding interventions included cuddling and back-patting[24] or swaddling, sidelying, swinging, shushing, and sucking[25] by a clinician. The way parents usually comfort their infants after vaccination was the comparison condition. There was low quality evidence and a benefit of the holding intervention was observed for both measures of distress evaluated: acute procedure distress and acute and recovery procedure distress combined (see Table http://links.lww.com/CJP/A289 and Figure, http://links.lww.com/CJP/A303 SDC 8). In the analysis including data from both studies (ie, distress during the acute and recovery phases) (n = 417 infants), the SMD was −0.65 (95% CI: −1.08, −0.22).

Should Sitting Upright be Used (Rather Than Lying Supine) During Vaccine Injections in Children Above 3 Years and Adults?

In 1 trial including children aged 4 to 6 years, sitting upright was compared with lying supine.[26] Pain and fear were critically important outcomes, and for both, the quality of evidence was low (see Table, http://links.lww.com/CJP/A290 SDC 9). The results were mixed: children in the sitting upright group reported lower levels of fear than those lying supine group postintervention (ie, after positioning but before the procedure) (n = 107): SMD −0.39 (95% CI: −0.77, −0.01); pain from vaccination, however, did not differ significantly between groups: SMD 0.07 (95% CI: −0.31, 0.45). Given the young age range of the children that participated and the possibility of difficulty with self-report in this age group, we also examined distress. There was a significant reduction in acute and recovery period distress combined in the intervention group: SMD −10.3 (95% CI: −20.18, −0.42) (see Table http://links.lww.com/CJP/A290 and Figure, http://links.lww.com/CJP/A304 SDC 9).

Should Non-nutritive Sucking (eg, Finger/Thumb, Pacifier) be Used During Vaccine Injections in Children 0 to 2 Years?

Two studies including infants from 0 to 4 months of age were included in the systematic review.[27,28] There was low quality evidence across the different outcomes of distress that were evaluated and evidence of benefit for all of them (see Table http://links.lww.com/CJP/A291 and Figure, http://links.lww.com/CJP/A305 SDC 10). In the only analysis including both studies (n = 186 infants), the SMD was −1.88 (95% CI: −2.57, −1.18) for the outcome of acute distress. The rate of sucking may be important for effectiveness; included studies did not determine sucking rate.

Should Manual Tactile Stimulation be Used During Vaccine Injections in Individuals of All Ages?

Altogether, 6 studies investigated the effects of manual tactile stimulation versus no treatment on vaccine injection pain in infants, children, and adults.[29–34] The intervention was delivered in various ways, including; manual pressure, rubbing/stroking, and tapping. The clinician delivered the intervention in all but 1 study, which used a parent instead.[30] There was moderate to very low quality evidence for critical outcomes (pain and distress) (see Table, http://links.lww.com/CJP/A292 SDC 11). For 3 studies including an evaluation of self-reported pain (n = 893),[29,32,33] there was insufficient evidence of a benefit of manual tactile stimulation: SMD −0.38 (95% CI: −0.96, 0.21). In the remaining 3 studies in infants,[30,31,34] there was no evidence of a benefit across indicators of distress, even when the study including parents as the deliverers of the intervention[30] was excluded. In the only analysis that included all studies (n = 301 infants), the SMD was −0.69 (95% CI: −1.77, 0.39) for acute distress (see Table http://links.lww.com/CJP/A292 and Figure, http://links.lww.com/CJP/A306 SDC 11). The evidence base included heterogeneity in the delivery of the intervention, type of injection, and cointerventions.

Should Tactile Stimulation Using an External Vibrating Device and Cold be Used During Vaccine Injection in Children Above 3 to 17 Years?

Two studies including children aged 4 to 7 years investigated the effect of externally applied vibrating devices with cold.[35,36] In 1 study, a multifaceted tactile intervention was used whereby a vibrating device was applied to the contralateral arm in the form of a game, and an external tactile device was pressed on the skin on the ipsilateral side. In addition, a vapocoolant was sprayed on the vaccination site immediately before injection with a verbal suggestion of diminished sensation.[35] In the other study, a vibrating device decorated as a bee with an ice pack attached to the underside (Buzzy) was applied by a researcher on the arm being vaccinated just above the injection site and kept there until the end of the injection.[36] The quality of evidence for the critical outcomes (pain, fear) was low (see Table 12, http://

links.lww.com/CJP/A293 SDC 12). There was a benefit of the vibrating device plus cold on pain (n = 145): SMD −1.23 (95% CI: −1.58, −0.87). There was no evidence of a benefit for fear (n = 104): SMD 0.28 (95% CI: −0.11, 0.66) (see Table http://links.lww.com/CJP/A293 and Figure, http://links.lww.com/CJP/A307 SDC 12). The contribution of cold and distraction to the effectiveness of both of these tactile interventions is not known.

Should Warming the Vaccine Before Vaccine Injections be Used in Individuals of All Ages?

One study evaluated the effect of warming the vaccine on vaccine injection pain in 150 adults.[37] Vaccines warmed by rubbing with hands or by inserting into an incubator immediately before injection were compared with no warming. Because of similarities in the temperature of the vaccine achieved with both warming techniques (27 and 29°C, respectively), the data were combined and compared with the no warming group (19°C). There was low quality evidence for the critical outcome of pain and pain did not differ between those that received the warmed vaccine versus those that received unwarmed vaccine: SMD 0.02 (95% CI: −0.32, 0.36) (see Table http://links.lww.com/CJP/A294 and Figure, http://links.lww.com/CJP/A308 SDC 13).

Should Muscle Tension be Used for Vaccine Injections in Children 7 Years and Above and Adults With a History of Fainting?

Three studies including individuals in mid to late adolescence through adulthood were included; none of the studies evaluated the vaccination context.[38,39,40] Muscle tension was achieved using a variety of physical maneuvers and both cyclical (muscle tension then release and repeat) and holding (continuous tension) methods were used. Some training was provided (eg, demonstration, instruction, practice with biofeedback, photos of maneuvers, supervision, and feedback). The critical outcome was fainting. Two of the studies were included in the meta-analysis[38,39] and fainting was assessed in these studies using a tilt-table test or year-long follow-up of everyday life. The results were mixed for different indicators of fainting and the quality of evidence was very low (see Table http://links.lww.com/CJP/A295 and Figure, http://links.lww.com/CJP/A309 SDC 14). Muscle tension resulted in benefits in the number of individuals fainting acutely during a procedure (n = 38; RR: 0.11 [0.02, 0.79]), number of individuals fainting over a 1-year period (n = 208; RR: 0.62 [0.44, 0.88]), and number of fainting episodes/individual/year (n = 208; SMD: −3.32 [95% CI: −3.74, −2.90]). It did not demonstrate a benefit on postprocedural fainting (although the tension had ceased at that time), or time to recurrence at follow-up.

DISCUSSION

This systematic review was undertaken to determine the effectiveness of different procedural and physical interventions that can be used by immunizers to reduce pain, fear, distress, fainting related to vaccine injections, or more than one. There was some evidence to support the following interventions in select populations: no aspiration during IM injections, injecting the most painful vaccine last when multiple vaccines are injected, simultaneous injections rather than sequential injections, IM injection into the vastus lateralis rather than the deltoid, positioning interventions (skin-to-skin contact, holding, or upright positioning rather than lying supine), non-nutritive sucking, tactile stimulation using an external vibrating device and cold, and muscle tension. There was insufficient evidence to support warming the vaccine before injection and manual tactile stimulation.

The results were mixed regarding the impact of no aspiration for IM vaccine injections. In 1 study including adolescents and adults,[12] there was no evidence of a benefit of avoiding aspiration on self-reported pain, whereas in the other studies including infants,[10,11] there was a benefit on measures of infant distress. The discrepant results in the former study may be explained by differences in study design and execution, including: use of a particularly painful vaccine,[54] insufficient time for aspiration, and variability in anatomic site of injection. As aspiration is not a necessary step of IM vaccine injections[55] and incurs additional needle dwelling time to ensure it is undertaken appropriately with the potential for wiggling of the needle within the tissue, additional tissue damage and pain, there is no rationale for performing it. It is unclear whether the results in the latter studies were confounded by differences in injection speed as the no aspiration technique was coupled with a fast injection (vs. aspiration with slow injection). The specific impact of injection speed requires further study.

This review found that injecting the most painful vaccine last when 2 vaccines are administered sequentially results in less pain. The findings are consistent with animal and human studies demonstrating a relationship between future pain and previous pain, and increasing pain after repeated noxious sensory stimulation.[56–60] These results, however, are limited to the combinations of vaccines that were evaluated in included studies. Additional studies are needed to determine the relative "painfulness" of other vaccines that are routinely given in combination to provide more complete guidance to immunizers with respect to the order of their administration to minimize pain.

Another intervention with some evidence of a benefit in the context of multiple separate vaccine injections is simultaneous injections. Simultaneous injections were demonstrated to reduce infant distress. However, there was no observable benefit in children. It is possible that children become fearful when approached by 2 immunizers and that this counteracts any benefit of the intervention in this age group. It is important to note that infants begin to develop "stranger anxiety" in the presence of unknown adults that may be exacerbated in the presence of a greater number of unknown adults needed to deliver this intervention, which could increase distress; in such cases, alternatives to this intervention should be considered. Stranger anxiety is developmentally normal and tends to be present in infants above 6 months.[61] Additional resources (ie, multiple immunizers) are also required to deliver this intervention making feasibility an issue.

The vastus lateralis is a muscle situated on the outer aspect of the upper thigh and is currently recommended as the primary site of vaccination for infants.[55] One study compared infant distress from vaccine injection in the vastus lateralis versus the deltoid,[18] a muscle in the upper arm—the preferred vaccination site in older children and adults.[55] There was some evidence of benefit on infant distress, providing support for the vastus lateralis as the primary site for vaccination of infants. There were no other studies that compared the effects of alternative anatomic sites of injection on pain. There are, however, observational studies reporting on preferences or actual uptake of vaccines according to the route of administration. In these studies, the intranasal route was preferred over the IM route.[62–64]

There was clear evidence of a benefit of skin-to-skin contact for reducing vaccine injection pain in neonates. These results are consistent with a recent meta-analysis of skin-to-skin contact for procedural pain in neonates.[65] The effectiveness of this intervention when applied by individuals other than the mother (eg, father) in the context of vaccination, however, is not known. In limited data in hospitalized neonates undergoing other needle procedures, there was no evidence of a difference when this intervention was delivered by a different individual, including the father or an alternate female.[65]

There was some evidence of a benefit of holding during vaccine injections in infants after removal of the data from 1 study from the meta-analysis that included contamination of the control group.[23] The optimal holding position, however, is not known and may depend on infant preferences; holding in a parent's lap in a gentle hug with the child's legs on either side of the parent may be one way to deliver this intervention that results in child comfort and keeps limbs still without leading to undue restraint (that can further increase distress).[66] A combined holding intervention administered after injection was also demonstrated to reduce infant distress. The intervention consisted of cuddling and back-patting[24] or swaddling, side-lying, swinging, sucking, and shushing.[25] In included studies, however, the holding intervention was delivered by a clinician and parents would have to be trained to deliver the intervention to make it a feasible intervention across clinical settings. Of note, close proximity soothing is regarded as a developmental need for infants in distress.[67]

There was a benefit of sitting upright on children's self-reported fear in 1 study included in the systematic review.[26] It has been hypothesized that individuals are less afraid when sitting up than lying down and sitting up has been recommended for children as soon as they can maintain head and trunk control.[66,68] As with infants, methods of positioning that effectively comfort and secure limbs without undue force are recommended for children. This may include sitting on a parent's lap. Of note, in included studies, parents also preferred to have their children sitting up for injections and there was no evidence of an increase in the duration of the procedure.[26]

Non-nutritive sucking was demonstrated to reduce infant distress during vaccination. This is consistent with the findings of a separate systematic review of procedural pain management in neonates including non-nutritive sucking.[69] The mechanism underlying the effectiveness of non-nutritive sucking is not known, but may involve blocking the perception of pain, distraction, or both.[70] The rate of sucking may be important for effectiveness; included studies, however, did not determine the sucking rate. This intervention is suitable for infants that regularly use pacifiers. An adult may also be required to gently hold the device in place to stimulate sucking and to prevent it from falling out of the child's mouth. It is important to note that some infants may refuse to suck and should not be forced to do so as it may increase distress.

There was no evidence of a benefit of manual tactile stimulation. The proposed mechanism of tactile stimulation as a pain treatment involves the gate control theory of pain and the notion that the touch sensation competes with the pain sensation to reduce the pain signal to the brain.[71] There are several possible reasons for the lack of observed effect of manual tactile stimulation, including: (1) discomfort induced by the intervention due to excessive pressure, other aversive aspects of intervention delivery, or both; (2) fear induced by proximity of the immunizer and increased attention to the vaccination procedure by the individual; and (3) cointervention due to tactile stimulation being applied when holding infants and children or when securing limbs before vaccine administration, concurrent tactile stimulation applied during actual vaccine delivery (eg, pinching or pressing on the skin), or both. Together, these factors may have obscured or reduced any observable benefit of this intervention.

There was, however, a benefit observed for tactile stimulation when delivered to children undergoing vaccine injections using an external vibrating device coupled with cold. It is likely that the effectiveness of this intervention involves more than 1 mechanism. Distraction, cold, and suggestion may all have played a role in the effectiveness of this intervention. Separately, significant benefit of the intervention has been observed in children up to 18 years undergoing venipuncture.[72,73] Limitations for the use of this intervention includes the need for additional resources to deliver them, including supplies (vibrating devices) and personnel (to administer it). One recent study trained parents to administer the intervention to avoid the need for additional personnel.[74] Finally, consideration should be given to the cold sensation produced with this intervention (ie, vapocoolant spray or Buzzy) as it may lead to discomfort in some individuals.[2,75,76] It is possible to deliver the tactile component of both interventions without the cold component although the effectiveness of this is not known.

Warming the vaccine was not demonstrated to impact pain. The proposed mechanism for this intervention is that cold solutions stimulate nociceptors.[77] It is possible that the temperature achieved in the warming group, which was $< 30^{\circ}C$, was not sufficiently close to the body temperature to prevent pain. In a previous meta-analysis of warming local anesthetic solutions before injection, a significant reduction was demonstrated when body temperature ($\geq 37^{\circ}C$) was attained during warming of the solution.[77] In contrast, it is possible that the temperature achieved in the control group, which was approximately room temperature, may have been sufficiently high compared with usual refrigerated vaccine temperatures that it approximated an active treatment and was not sufficiently cooler than the warmed vaccine for warming to have demonstrated a benefit. Because of the lack of observed benefit of warming from the included trial, warming of vaccines is not recommended. It is important to additionally note that correct storage and handling temperatures are of paramount importance in maintaining biological activity of vaccines and that warming may impact vaccine effectiveness.

Pain and seeing blood, needle procedures, or both are included in the top 5 triggers for fainting.[78] Muscle tension combats the vasovagal response that otherwise leads to fainting by increasing blood pressure and cerebral blood flow. In this intervention, individuals learn to tense muscles of the body and can also learn the signs of a drop in blood pressure (ie, prodromal vasovagal signs) so that the tension technique can be utilized to prevent the onset of symptoms, or both arrest them once they appear. There was evidence for the effectiveness of muscle tension with respect to fainting both acutely during a procedure and number of fainting episodes per patient per year. Although the evidence base did not include vaccine injections specifically, there is no reason to believe that results would be different in this context; muscle tension has also reduced fainting responses in volunteer blood donors.[79] The use of muscle tension in vaccination contexts should be addressed in future research, including training of individuals on the spot. Caution is recommended with respect to positioning during vaccine injections to avoid falls; supported or a reclined sitting position are possible options.

A major limitation of the findings from this knowledge synthesis is the scant evidence base that exists for most of the evaluated interventions. Considering the vast number of vaccine injections that are performed worldwide and the fact that they occur in individuals of all ages, it is surprising that such little empiric evaluation of physical and procedural interventions has been undertaken. There is the possibility that some trials may have been missed, however, this risk was reduced by having a broad search strategy including gray literature (theses), articles published in other languages, and involving 2 reviewers in screening citation lists.[3] The risk of bias was high for all included trials, leading to uncertainty in the internal validity of the findings. In most cases it was difficult to blind personnel, such as immunizers, to the intervention. In addition, included studies often evaluated individuals of limited age ranges, and it is unclear that the results can be extrapolated to other ages. Strengths of the analysis, however, include the rigorous approach that included both GRADE and Cochrane methodologies, and a comprehensive approach to data synthesis that utilized the results of multiple outcome measures assessing the same construct within studies and combined data across studies. A priori, the effectiveness of specific interventions was analyzed separately to account for differences in intervention characteristics (eg, delivery) and developmental stage. This allowed for more fine-grained examination of intervention effectiveness. Other aspects of the methodological approach used in this systematic review are reviewed separately in another manuscript in this series.[80]

In conclusion, there are a variety of procedural and physical interventions that clinicians can use to improve the quality of pain care in individuals undergoing vaccine injections. Implementation of these interventions is contingent on the ability and willingness of vaccinators to use them. To this end, government agencies and educational institutions are encouraged to develop policies and resources that facilitate uptake of these interventions across practice settings. In addition, additional research is recommended to expand and strengthen the evidence base. New technologies are also warranted, including: adjustment of physicochemical characteristics of new vaccines to be less painful, combination vaccines, microneedles, and needle-free vaccine approaches (such as oral, transdermal, mucosal, and inhalational).

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